

# The role of the hippocampus in the pathophysiology of major depression

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Converging lines of research suggest that the hippocampal complex (HC) may have a role in the pathophysiology of major depressive disorder (MDD). Although postmortem studies show little cellular death in the HC of depressed patients, animal studies suggest that elevated glucocorticoid levels associated with MDD may negatively affect neurogenesis, cause excitotoxic damage or be associated with reduced levels of key neurotrophins in the HC. Antidepressant medications may counter these effects, having been shown to increase HC neurogenesis and levels of brain-derived neurotrophic factor in animal studies. Neuropsychological studies have identified deficits in hippocampus-dependent recollection memory that may not abate with euthymia, and such memory impairment has been the most reliably documented cognitive abnormality in patients with MDD. Finally, data from imaging studies suggest both structural changes in the volume of the HC and functional alterations in frontotemporal and limbic circuits that may be critical for mood regulation. The extent to which such functional and structural changes determine clinical outcome in MDD remains unknown; a related, but also currently unanswered, question is whether the changes in HC function and structure observed in MDD are preventable or modifiable with effective treatment for the depressive illness.

Des pistes de recherche convergentes indiquent que le complexe hippocampique (CH) peut avoir un rôle à jouer dans la pathophysiologie du trouble dépressif majeur (TDM). Même si des études postmortem révèlent peu de mort cellulaire dans le CH de patients déprimés, des études animales indiquent que des concentrations élevées de glucocorticoïdes associées au TDM peuvent avoir un effet négatif sur la neurogénèse, causer des dommages excitotoxiques ou avoir un lien avec la baisse des concentrations de neurotrophines clés dans le CH. Les antidépresseurs peuvent contrer ces effets, car on a démontré au cours d'études animales qu'ils élèvent la neurogénèse dans le CH et les concentrations de facteurs neurotrophiques d'origine cérébrale. Des études neuropsychologiques ont révélé des déficits de la mémoire du souvenir dépendante de l'hippocampe que l'euthymie peut ne pas réduire, et ces déficits de la mémoire constituent les anomalies cognitives les mieux documentées chez les patients atteints de TDM. Enfin, des données tirées d'études d'imagerie indiquent à la fois des changements structurels du volume du CH et des altérations fonctionnelles des circuits frontotemporaux et limbiques qui peuvent jouer un rôle crucial dans la régulation de l'humeur. On ne sait toujours pas dans quelle mesure ces changements fonctionnels et structurels déterminent l'issue clinique du TDM. Une question connexe mais à laquelle il n'y a toujours pas de réponse vise à déterminer si les changements de la fonction et de la structure du CH observés dans des cas de TDM sont évitables ou modifiables par des traitements efficaces contre la maladie dépressive.

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## Introduction

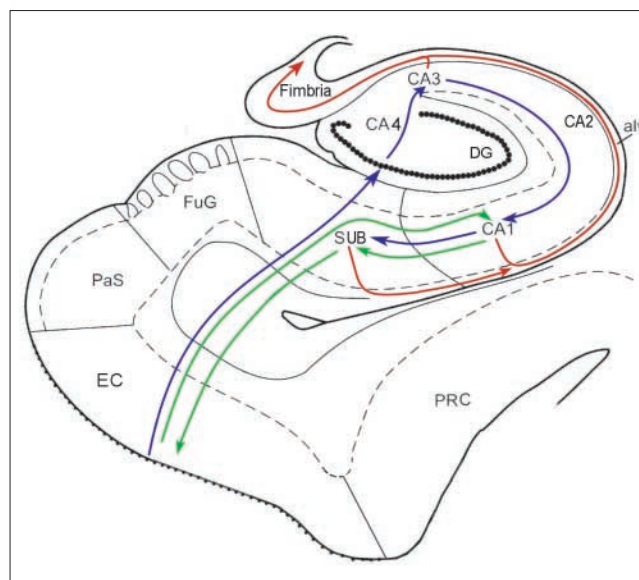
The behavioural and mood abnormalities associated with mood disorders appear to arise as the result of disturbances in a temporolimbic–frontal–caudate network.<sup>1,2</sup> Normal regulation of mood may depend on the integrity of pathways linking the paralimbic frontal cortex and the basal ganglia. Some investigators differentiate the orbitofrontal–amygdalar network that supports emotions and moods from the hippocampal–cingulate system that supports memory encoding and explicit processing, among other functions, but these 2 systems act in concert. Thus, a number of regions appear central to understanding the pathophysiology of mood disorders. The hippocampus is one region that has recently received significant attention in mood disorders research and, although almost certainly not solely responsible for the myriad of symptoms observed in depression, the highly plastic, stress-sensitive hippocampal region may play a central role in depressive illness.

Caudal to and intimately connected with the amygdala, the hippocampus is a bilaminar grey-matter structure that forms the floor of the inferior temporal horn of the lateral ventricle and extends from the anterior margin of the ventricular horn to the splenium of the corpus callosum. The laminae that make up the hippocampal complex (HC) consist of the dentate gyrus and the hippocampus proper, the cornu Ammonis. The latter, when observed in coronal sections, can be divided into regions, termed CA1–CA4, based on pyramidal neuron morphology and sensitivity to anoxia.<sup>3</sup> The glutamatergic pyramidal and granule cells represent 90% of hippocampal neurons, and the remaining 10% are primarily  $\gamma$ -aminobutyric acid (GABA)-producing interneurons.<sup>4</sup> Acetylcholine nicotinic receptors<sup>5</sup> and noradrenaline and serotonin (5-HT)<sup>6</sup> and 5-HT<sub>1A</sub> and 5-HT<sub>4</sub> receptors<sup>7,8</sup> in the CA1 region indicate the presence of other well-characterized neurotransmitters in the cornu Ammonis.<sup>9</sup>

The entorhinal cortex provides the major glutamatergic afferents to form synapses either directly on the pyramidal neurons of the CA1 region or to offer boutons to the dendrites of the granule cells of the dentate gyrus region. Mossy fibres originating from the granule neuron cells project to the dendrites of CA3 pyramidal cells, which in turn project to the CA1 region. Axons from the CA1 region contacted either directly or indirectly from the entorhinal cortex form at least 2

possible paths: (1) efferent projections to the subiculum, then through the fornix and the anterothalamic nucleus, or (2) efferent projections to the entorhinal cortex<sup>3</sup> through which the hippocampal output fibres reach the inferior temporal association cortex, the prefrontal cortex and the temporal pole<sup>10</sup> (Fig. 1). The HC also influences the ventral striatal loop via the nucleus accumbens.

The hippocampus is involved in learning and in consolidation of explicit memories from short-term memory to cortical memory storage for the long term; its precise role in memory storage remains an active area of research and is beyond the scope of this review. Loss of pyramidal neurons of the CA1 region of the HC is sufficient to cause moderate-to-severe anterograde amnesia, and damage limited to the HC and the entorhinal



**Fig. 1: Intrahippocampal pathways.** The green line represents the direct intrahippocampal pathway from layer 3 of the entorhinal cortex (EC) to the CA1 region and then to the subiculum (SUB). From the subiculum, information can return to the entorhinal cortex or can enter the alveus (alv) and then the fimbria to influence neurotransmission in other cortical regions (red line). The afferent polysynaptic pathway is represented by the blue line. Axons from the entorhinal cortex enter the dentate gyrus (DG), and dendrites from the granule cells contact these glutamatergic axons. The mossy fibres of the granule cells project to the pyramidal neurons of the CA3 region, which then gives rise to efferent fibres to the alveus (in red) or Schaffer collateral fibres to the CA1 region. The pyramidal cells of the CA1 region, the primary output region of the cornu Ammonis, can project to either the subiculum (blue) or the alveus (red). Other regions displayed here include the perirhinal cortex (PRC), the parasubiculum (PaS) and the fusiform gyrus (FuG).

cortex has been associated with retrograde and anterograde amnesia.<sup>11–13</sup> The evidence suggests that the HC itself can be divided functionally along the septotemporal axis. Lesions of the dorsal HC of rats, corresponding to the posterior HC in primates, result in a greater impairment of spatial memory than corresponding lesions in the ventroanterior HC.<sup>14</sup> Neurotoxic lesions of the ventral subiculum, an output region of the HC, appear to remove the negative feedback inhibition that the HC exerts on the hypothalamus, and elevated glucocorticoid levels are observed.<sup>15</sup>

### Cellular studies of the hippocampus in depression

Grey-matter structures, including the HC, are vulnerable to atrophy in disorders such as schizophrenia,<sup>16–22</sup> major depressive disorder (MDD),<sup>23–30</sup> bipolar disorder<sup>31</sup> and post-traumatic stress disorder.<sup>28</sup> Volume reductions of the HC might be the result of remodelling of key cellular elements, involving retraction of dendrites, decreased neurogenesis in the dentate gyrus and loss of glial cells.<sup>2,32–35</sup> Factors underlying this cellular remodelling include stress-induced elevated glucocorticoid levels, which are implicated in decreased neurogenesis<sup>36</sup> and induce cell cycle arrest in the peripheral cells.<sup>37</sup> Glucocorticoids eliminate activity-dependent increases in brain-derived neurotrophic factor (BDNF) levels,<sup>38</sup> potentially making the neuron morphologically unresponsive to stimuli and inhibiting dendritic arborization. Increased activity of the hypothalamic–pituitary–adrenal axis resulting in elevated glucocorticoid levels combined with resistance to glucocorticoid-induced negative feedback control is commonly seen in MDD.<sup>39–42</sup> This dysregulation of glucocorticoid secretion with increased activity of excitatory amino acid neurotransmitters could result in both potentially reversible remodelling and irreversible cell death in the HC of patients with MDD.<sup>43</sup> As the hippocampus has a role in negative feedback inhibition of glucocorticoids,<sup>44</sup> remodelling or neuronal damage may lead to less efficient inhibitory control of the corticotrophin-releasing hormone, producing cells of the hypothalamus, resulting in increased circulating glucocorticoids and further HC damage.<sup>45</sup> Both elevated glucocorticoid levels<sup>15</sup> and no significant changes in corticosterone concentrations<sup>46</sup> have been observed in response to lesions of the HC, though the former study showed the increase specifically after lesions in the subiculum region of the

HC. This suggests that there are regional differences within the HC tonic inhibition of adrenocortical activity. A decrease in survival and growth-promoting neurotrophic factors such as BDNF could lead to low HC volume and vulnerability to subsequent episodes of depression as a result of decreased neurogenesis, increased remodelling of dendrites and loss of glial cells or increased excitotoxicity.<sup>47</sup>

### Animal models of depression

The action of antidepressant medications may at least partially be produced through their effects on the HC.<sup>48</sup> Rat studies suggest that there may be a neuroprotective effect of antidepressant medications, because these agents can induce neuronal sprouting and neurogenesis.<sup>49</sup> Antidepressant treatment results in increased levels of BDNF in the dentate gyrus and the CA3 region of the HC of treated rats that are stressed during early life by maternal separation.<sup>50</sup> Long-term treatment with antidepressant medications is thought to act on monoamine systems to increase basal and stimulated adenylate cyclase activity,<sup>51</sup> increase cyclic adenosine monophosphate (cAMP)-dependent phosphorylation<sup>52</sup> and increase cAMP response element-binding protein (CREB) mRNA levels in the CA1, CA3 and dentate gyrus regions of the HC.<sup>53</sup> Upregulation of CREB may be a common target of serotonergic and noradrenergic systems, the neurotransmitters that have to date been studied most with respect to MDD.<sup>54,55</sup> CREB modulates BDNF production, and BDNF mRNA decreases in the HC after repeated stress.<sup>56</sup> Antidepressant medications upregulate BDNF<sup>57</sup> and its receptor trkB<sup>58</sup> and block stress-related downregulation of BDNF.<sup>51</sup> These effects occur after long-term treatment with antidepressant medications. Thus, animal and cellular studies suggest that antidepressant medications may protect HC integrity, but only 1 preliminary study in humans has suggested that these effects translate in patients into maintained HC structural integrity.<sup>59</sup>

### Postmortem studies of patients with depression

Changes in glial cell density and decreased neuronal size have been reported in postmortem specimens from the prefrontal cortex of patients with MDD.<sup>60–62</sup> Extreme stress and consequent severe glucocorticoid exposure are associated with changes in the gross cellular morphology of the HC in the rat and in nonhuman

primates;<sup>63-65</sup> however, evidence for gross hippocampal changes in human patients with MDD is lacking.<sup>66,67</sup> It is not known whether this reflects limitations of the postmortem studies in failing to account for depressive burden, treatment history, age at onset of depression and heterogeneity in the causes of depression in samples studied to date. Postmortem studies of patients with schizophrenia, with changes in HC volume similar to those seen in MDD, have also failed to find reliable changes in HC neuronal number, density, orientation or size.<sup>68,21</sup> Although moderate apoptosis has been observed in the dentate gyrus and the CA1 and CA4 regions of the HC of patients with MDD,<sup>66</sup> this can only partially account for observed volumetric changes. These studies have not recorded whether the subjects were between depressive episodes; it is possible that patients experience some HC recovery in the inter-episode period, thus obscuring evidence of atrophy if death occurs when patients are relatively free of depressive symptoms. Studies of patients with Cushing's disease do suggest that HC volume and function can undergo recovery when glucocorticoid levels return to normal.<sup>69</sup>

## Magnetic resonance imaging studies of the hippocampus in depression

In some ways the most provocative, but also the most controversial, data linking the HC to MDD have been from magnetic resonance imaging studies of the volume of the HC in patients with MDD; these studies are summarized in Table 1.<sup>23-27,29,30,70-75</sup> Despite variation in the measurement techniques and patient samples, when we combined results from studies measuring the HC alone using a meta-analytic technique, we showed that depressed patients had significantly decreased left and right hippocampal volumes compared with controls (Fig. 2).<sup>76-79</sup>

Genetic vulnerability, early abuse and chronic stress predispose individuals to depression. These factors might also predict a small HC in samples of depressed patients with these variables. The possibility that a small HC may predate onset of psychiatric illness has not been evaluated in samples of patients with strong family histories of MDD. The notion that a small HC may confer vulnerability to stress-associated disorders, however, has been recently assessed in a study of

**Table 1: Magnetic resonance imaging studies of hippocampal volume in depression**

Study	Statistically significant changes in HC volume	Mean age, yr	No. of subjects	Patients		No. of subjects	Controls	
				Mean hippocampal volume, mm <sup>3</sup>			Mean hippocampal volume, mm <sup>3</sup>	
				L	R		L	R
Posener et al <sup>70</sup>	No	33	27	2546	2948	42	2475	2994
MacQueen et al <sup>23</sup>								
Multiple past episodes of depression	↓L and R	32	17	2381	2392	17	2703	2692
First episode of depression	No	28	20	2738	2793	20	2761	2784
Vythilingam et al <sup>24</sup>								
Past abuse	↓L	33	21	2705	2690	14	3179	3037
No past abuse	No	34	11	3292	3078	14	3179	3037
Frodl et al <sup>25</sup>	↓L*	40	30	3564	3745	30	3616	3641
Rusch et al <sup>71</sup>	No	33	25	2170	2290	15	2130	2200
Steffens et al <sup>26</sup>	↓R	72	66	2920	2980	18	3170	3300
Bremner et al <sup>72</sup>	↓L	43	16	940	982	16	1166	1113
Mervaala et al <sup>27</sup>	↓L	42	34	3104	3462	17	3441	3700
Vakili et al <sup>73</sup>	No	38	38	2640	2610	20	2460	2600
Von Gunten et al <sup>74</sup>	No	58	14	2499	2598	14	2644	2700
Ashtari et al <sup>75</sup>	No	74	40	1745	1742	46	1843	1853
Sheline et al <sup>29</sup>	↓L and R	54	24	2230	2264	24	2482	2468
Sheline et al <sup>30</sup>	↓L and R	68	10	2159	2283	20	2544	2577

Note: HC = hippocampal complex; L = left; R = right.

\*Statistically significant difference between LHC of patients and controls seen only in men.

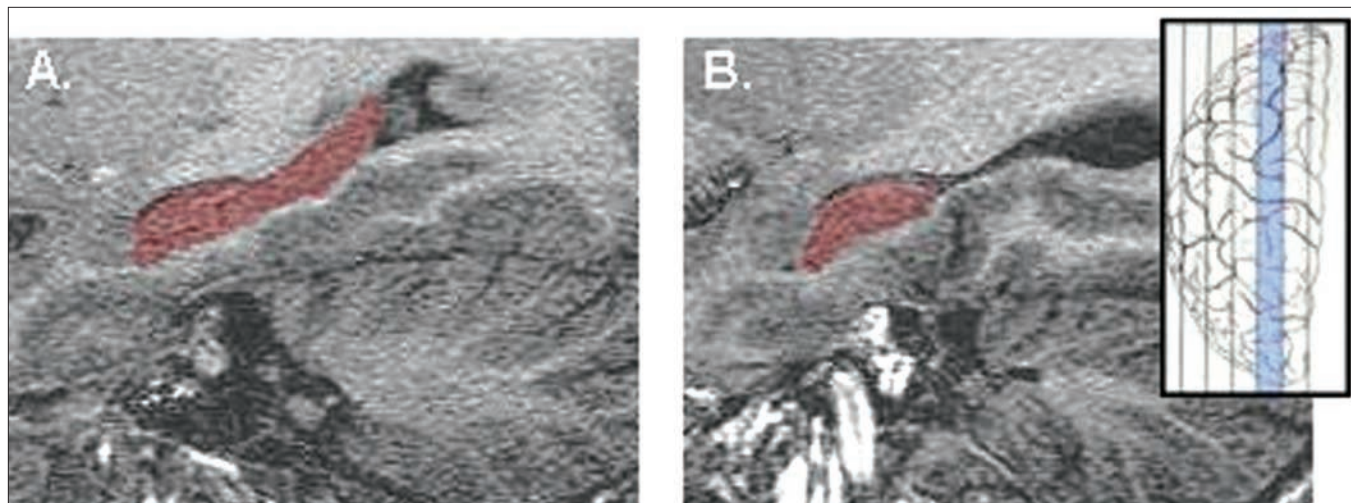


individuals exposed to combat who had nonexposed monozygotic twins. HC volume in the trauma-exposed *and* in the nonexposed, asymptomatic twin correlated negatively with severity of post-traumatic stress disorder in the twin who had been exposed to trauma.<sup>80</sup> These data suggest that genetic factors lead to small HC volumes and confer vulnerability to psychiatric illness as a consequence of this reduction. Whether genetic vulnerability is expressed in part through a small HC that confers vulnerability to MDD is unknown, but the sample in which this may be most readily tested comprises individuals with strong family histories of MDD.

A literature beyond the scope of this summary has established the association between early trauma or abuse and depression.<sup>81</sup> Several recent studies have focused on early abuse and HC function and volume in MDD. Vythilingam et al<sup>24</sup> recently studied 21 women with a significant history of prepubertal physical or sexual abuse and current MDD. Prepubertal abuse is associated with long-term dysregulation of the hypothalamic–pituitary–adrenal axis, in contrast to postpubertal abuse, for which such an association has been less consistently described. Depressed women with past abuse had a 15% reduction in left HC volume compared with healthy control subjects; in contrast, women with MDD but no history of abuse had HC

volumes similar to those of healthy controls. These data are consistent with those from other studies that examined women who had a history of prepubertal abuse; in general, past abuse is associated with reduced HC volume.<sup>24,81,82</sup> Unfortunately, the samples of women studied to date have been heterogeneous with respect to past severity, duration and treatment history of depression. Therefore, although it appears that prepubertal abuse may be associated with reduced HC volume, it may also be the case that prepubertal abuse is associated with severe or recurrent depression, which results in reduced HC volume.

Chronic or recurrent depressive episodes may also lead to HC volume reduction. Sheline et al<sup>29</sup> reported that total duration of past illness predicted degree of HC volume reduction when duration of illness was assessed as number of days spent ill; others have reported that volumetric reductions were greater in patients with a chronic course of depression and a large number of weeks spent ill compared with those who recovered fully with a shorter overall duration of illness,<sup>83</sup> although not all investigators have reported such a relation.<sup>72</sup> Our cross-sectional study of patients with either a first episode or multiple past episodes of depression suggested that patients with multiple episodes were more likely to have smaller HC volumes; a nonlinear relation between HC volume and number of past



**Fig. 2:** Magnetic resonance spectroscopic images of the left hippocampus in a healthy control subject and in a patient with recurrent depression. The size of the difference shown here is unusually large, with most positive studies reporting a reduction in hippocampal complex (HC) volume of about 15% between cases and controls.<sup>78</sup> Insert shows in blue the approximate sagittal level of the HC. Images were acquired on a 1.5-T GE Sigma Genesis–based EchoSpeed imager using previously published parameters.<sup>79</sup>

**A:** Sagittal view of the left HC, highlighted in red, of a healthy control subject whose left HC volume measured 3295 mm<sup>3</sup>. **B:** The patient whose left HC is represented here, with an HC volume of 2015 mm<sup>3</sup>, was of the same age and sex as the control subject but had a long history of recurrent depression.

episodes further suggested that most of the volume loss occurred within the first few episodes.<sup>23</sup> These data are consistent with recent reports that patients with schizophrenia have the greatest volumetric changes in the period shortly after onset of illness.<sup>84</sup> A key related question is whether effective treatment starting early in the illness can slow or prevent the rate of volume loss in this illness. A recent study reported an association between HC volume loss and time spent with untreated depression but no association between HC volume and time during which depression was being treated, suggesting that volume loss may be arrested by antidepressant treatment.<sup>59</sup> Further studies are necessary to clarify whether, in fact, effective treatment can minimize HC volume loss. Further studies are also required to reconcile the observed volume reductions in imaging studies with postmortem studies that have reported only moderate apoptosis in this region.<sup>66</sup> It is possible, for example, that cell loss by apoptosis is a significant event over many years of illness, whereas retraction of the neuron's dendritic tree might be observed earlier in the course of illness and might partially account for the observed volume loss with the lack of significant cell death in depressed patients.

### Neuropsychological studies of hippocampal function in depression

Discrete memory systems have now been classified.<sup>78,85</sup> Recollection memory, which is analogous to explicit or declarative memory, requires the conscious recall of specific facts or events. In contrast, habit memory, implicit memory and nondeclarative memory all refer to a memory system that uses unconscious skills or strategies.<sup>78</sup> The distinctions between these systems and the evidence that they are reliant on relatively independent brain structures have been extensively reviewed and debated. Evidence for the link between recollection memory and HC formation comes from studies of patients with HC damage,<sup>86-88</sup> animal studies<sup>89</sup> and many functional imaging studies that have greatly clarified the role of frontal and temporal regions in various memory systems.<sup>90-97</sup>

An effect size analysis of cognitive functioning in 726 patients with MDD conducted using meta-analytic principles found that depression had the largest effect on recollection memory<sup>98</sup> and little effect on habit memory, although evidence for this strict distinction has been controversial.<sup>99</sup> Most studies report that depressed

subjects perform as well as control subjects on implicit tasks,<sup>100-103</sup> but one study reported implicit memory deficits in depressed subjects.<sup>104</sup> Implicit memory tasks are potentially susceptible to the influence of explicit strategies, and differential use of explicit strategies in depressed and control groups may account for the apparent discrepancy on implicit tasks.

Further evidence for the proposal that recollection memory may be specifically impaired in depression comes from studies of working memory in depressed subjects. Working memory, that is, the ability to transiently maintain and use information, has been linked to the frontal cortex by both animal and human studies, and it has been reported to be abnormal in patients with psychotic disorders<sup>79,105,106</sup> and obsessive-compulsive disorder.<sup>107</sup> Studies of working memory in depressed patients, however, have failed to find differences in performance between patients and controls; working memory appears to be relatively spared in depression<sup>98</sup> and other mood disorders.<sup>108,109</sup> It is important to note that studies that assessed working memory and recollection memory tasks in the same subjects have found intact working memory but impaired recollection memory.<sup>110</sup> Such studies highlight the fact that depressed patients do not show equal impairment across memory systems; rather, increasing evidence supports the hypothesis that depressed patients show differential impairment on recollection memory tasks that are dependent on the HC. This specificity of impairment also suggests that motivational impairment of depressed individuals cannot readily account for decreased test performance on recollection memory tasks. Furthermore, recollection memory impairments can persist when patients attain euthymia, with presumably full recovery of the motivational state.

Interestingly, a recent positron emission tomography (PET) study used [<sup>11</sup>C]WAY100635 to examine 5-HT<sub>1A</sub> receptors and assess their relation with memory function. Postsynaptic 5-HT<sub>1A</sub> receptors localized in the HC were found to have a negative influence on explicit memory function.<sup>111</sup> These authors suggested that the antagonistic effect of postsynaptic 5-HT<sub>1A</sub> receptors in the HC could improve memory function, whereas administration of tandospirone, a 5-HT<sub>1A</sub> agonist, impaired explicit verbal memory in a dose-dependent manner. To date, there are no established strategies for treating the memory dysfunction associated with MDD, and this is particularly relevant given the evidence that such memory impairment persists into the euthymic state for many patients.

## Functional imaging studies of hippocampal function in depression

PET has been used extensively to evaluate the metabolic activity of discrete brain regions in depressed patients compared with healthy controls by observing the increased glucose uptake (metabolism) and regional blood flow resulting from metabolically active tissues. Three recent studies of regional cerebral glucose metabolism in subjects with MDD did not find differences in activity in the HC of depressed patients compared with controls.<sup>112–114</sup> Several reviews of earlier functional imaging studies in MDD do not discuss the HC in their overviews of regions that demonstrate cerebral blood flow changes in MDD.<sup>115–117</sup> In contrast, 2 reports by Videbech et al<sup>118,119</sup> demonstrate increased blood flow, and therefore increased regional metabolism, to the HC, the cerebellum, the anterior cingulate gyrus and the basal ganglia in depressed patients as compared with controls, with a correlation between the total Hamilton Depression Rating Scale score and blood flow to the HC.<sup>118</sup> Depressed patients also showed increased activity of the HC compared with the healthy controls when the results were corrected for the influence of antidepressant medication.<sup>119</sup>

PET studies designed to evaluate regional glucose metabolism in the HC of depressed patients after treatment with antidepressant medications have shown either a relative decrease<sup>120,121</sup> or no change,<sup>113</sup> as compared with untreated patients. Interestingly, a recent study by Mayberg et al<sup>121</sup> found a decrease in HC metabolism after treatment with fluoxetine that was not present in placebo-treated patients, although both groups of patients had equal numbers of responders. Other regions that showed fluoxetine-specific changes were the striatum and the brain stem. Overall, the extensive literature examining blood flow and cerebral metabolism in depressed patients has found a greater number of positive results for frontal and limbic regions, although some studies have also found parahippocampal changes. The significance of the studies that have reported metabolic changes to the HC in response to antidepressant treatment remains to be determined.

## Summary

Several brain regions, including the prefrontal cortex and the limbic and cingulate regions, may be central to the pathology of MDD. Several lines of research have

converged to support the notion of the HC being an important region in the pathophysiology of MDD. Data from animal and postmortem studies suggest that excitotoxic damage may occur to the HC after prolonged exposure to glucocorticoids and may result in long-lasting cellular alterations in this region. Data from volumetric imaging studies highlight the fact that clinical parameters of patients, such as early history, family history and burden of syndromal and subsyndromal illness, may make an important contribution to HC volume. Neuropsychological studies reliably report deficits in HC-dependent recollection memory that may not abate with euthymia. Functional imaging studies implicate frontotemporolimbic circuit changes in patients with MDD, but the results of these studies are variable with respect to observed changes in the HC. Despite these converging lines of evidence suggesting that the HC is important in the pathophysiology of MDD, including studies that suggest that there may be structural changes in this region, virtually nothing is known about whether appropriate early treatment of MDD can alleviate or even reverse some of these changes. Future studies will be important to clarify the association between HC integrity and clinical outcome and to examine potential strategies for maintaining HC integrity in patients with MDD and other psychiatric disorders.

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